

29 The pharmaceutical composition of Claim *27* wherein the antibody

29 contained therein is 24-31.---
AS

REMARKS

Entry of the foregoing amendments, reconsideration and reexamination of the subject application, as amended, pursuant to and consistent with 37 C.F.R. § 1.112, and in light of the remarks which follow, are respectfully requested.

Turning now to the Office Action, the objections to the specification have been noted. The spelling of the BALB/c mouse has been corrected in accordance with the Examiner's suggestion. Also, it is acknowledged that the drawings submitted with this application are formal. Moreover, the specification at page 1 has been amended to update the status of the cited commonly assigned applications. Based on the foregoing, withdrawal of the previous objections to the specification is respectfully requested.

Claims 9-17 and 20-21 stand rejected under 35 U.S.C. § 112 first paragraph as not being enabled. Essentially, the basis of this rejection is that it is unclear whether the disclosed antibodies (more specifically the corresponding cell lines) have been publicly deposited. It is believed that this rejection should be moot based on the present amendment which limits the subject claims to either monoclonal antibody 24-31, monoclonal antibody 89-76, or antibodies having equivalent binding specificity. This is believed to be the case as cell lines which secrete both of these antibodies have been publicly deposited.

Specifically the undersigned specifically avers herein, that cell lines which secrete these antibodies were deposited with the ATCC on September 2, 1994. The 24-31 hybridoma cell line and the 89-76 hybridoma cell line were respectively accorded ATCC Accession No. HB11712 and Accession No. HB11713. Further, applicants note that both of these hybridoma cell lines were deposited in accordance with the Budapest Treaty and will be redeposited should these deposits become nonviable during the term of this deposit. Still further, applicants aver that all restrictions as to the availability of the cell lines will be irrevocably removed upon issuance of a patent to this application. Therefore, based on the foregoing withdrawal of the 112 first paragraph rejection of Claims 9-17 and 20-21 is respectfully believed to be in order.

Claims 1-21 further stand rejected under 35 U.S.C. § 112 first paragraph as being broader than the enabling disclosure. Essentially, the Examiner stated that the claims should be limited to a specific gp39 protein, i.e. a protein having a specific effector function and polypeptide structure. This rejection is respectfully traversed to the extent that it may be applicable to the claims as amended.

At the outset, it is respectfully noted that the claims now clarify that gp39 corresponds to the CD40 ligand. Therefore, the claim has been amended substantially in accordance with the Examiner's suggestion. Such Amendment finds support from the as-filed disclosure which indicates that gp39 is a ligand for CD40. In fact, as indicated by the Examiner this is a well known equivalent term for gp39. Therefore, applicants respectfully submit that it would be clear to one skilled in the art as to what is intended by gp39, and therefore it would be clear as to what antigen the claimed monoclonal

antibodies bind. In this regard, it is proper to construe claims in light of the as-filed disclosure. Moreover, claims are to properly construed in light of the state of the art as it existed at the time of the invention. At the time this application was filed, numerous references had been published relating to gp39 and it was further well known that this antigen is known by various names, and corresponds to an antigen expressed on activated T cells which is involved in antibody effector function. Therefore, withdrawal of the 112 first paragraph rejection of Claims 1-21 is respectfully requested.

Claims 1-21 further stand rejected under 35 U.S.C. § 112 second paragraph as being indefinite. This rejection is also respectfully traversed to the extent it may be applicable to the claims as amended.

The assertion that gp39 is unclear is believed to be moot as the claim now clarifies that this corresponds to CD40 ligand. For the reasons set forth above, one skilled in the art would be well aware as to what is intended by gp39, particularly when the claims are construed in light of the as-filed disclosure.

Further, the recitation "3E4, 2H5, 2H8, 49-8, 49-9, 24-31, 24-43, 89-76 and 89-79" is asserted to be indefinite. This objection is also respectfully traversed to the extent it may be applicable to the claims as amended. In particular, the newly submitted Claims 22-30 only refer to monoclonal antibodies 24-31 and 89-76. The meaning of these specific antibodies would be readily apparent, as the claims clearly recite that these monoclonal antibodies are secreted by specific cell lines. Therefore, the claims uniquely identify which specific monoclonal antibodies are intended hereby. Therefore, withdrawal of the previous 112 second paragraph rejection is respectfully requested.

Claims 1-21 further stand rejected under 35 U.S.C. § 103 as being unpatentable over Lederman (U.S. Patent No. 5,474,771) or Lederman et al. (WO 93/08207) or Armitage et al. (WO93/09812) or Aruffo et al. (EP 0 555 880) or Aruffo et al. (EP 0 585 943), and further in view of well known procedures and usage of antibodies in B cell proliferation assays as disclosed in the subject application.

Essentially, the references cited by the Examiner, all relate to the identification of gp39, which is referred to by various names, and the generation of antibodies thereto having potential efficacy for inhibiting T cell induced B cell proliferation. For example, the Lederman references refer to gp39 as "the 5C8 antigen" and teach prophetically that antibodies to this protein may be used for inhibiting B cell proliferation and antibody responses. Further, the Aruffo et al. references similarly teach the role of the CD40 ligand in T cell induced B cell activation, and the use of antibodies thereto for inhibiting helper function and as therapeutics. Further, Armitage clones the CD40 ligand, and prophetically discloses the production of antibodies thereto.

However, none of these references teaches or suggest the specific monoclonal antibodies of the subject invention. In particular, while they generically suggest the production of monoclonal antibodies specific to the gp39 protein, they would not enable the specific monoclonal antibodies that bind human gp39 which are claimed herein.

Applicants respectfully advise that for a 103 rejection to be proper, the references alone or in combination must enable the claimed invention. This burden has not been met, as none of the references teaches or suggest the specific monoclonal antibodies claimed herein or corresponding cell line. Moreover, the rejection is not proper merely based on

the fact that well known procedures are available for producing monoclonal antibodies. While this is acknowledged, it is further noted that such techniques are unpredictable. Essentially, it is not known with respect to any given hybridization event what specific human monoclonal antibodies will be produced. Indeed, it is well known in the art that the production of monoclonal antibodies to specific proteins is highly empirical, and results in the generation of a myriad of different monoclonal antibodies having different characteristics including binding properties, amino acid sequences, effector functions, among other differences.

In view of this well known unpredictability, applicants respectfully submit that the 103 rejection based on the Lederman et al. references taken in view of Aruffo et al. and Armitage, alone or in combination with asserted well known procedures and uses of antibodies, should be withdrawn, as none of these references would enable the identification and isolation of the two specific monoclonal antibodies which bind human gp39 which are claimed herein. More specifically, none of these references would enable the specific isolation of 24-31 or 89-76 or a corresponding hybridoma cell line. Also, this argument is further supported by the § 112 enablement rejection where the Examiner concluded that the enablement of claims to these antibodies requires the availability of specific cell lines which are not taught by these references.

The unpredictability associated with the production of monoclonal antibodies is substantiated by the variable characteristics of the different monoclonal antibodies disclosed in the subject application. For example, it can be appreciated upon review of the information contained in Table 3, that of the six specific monoclonal antibodies

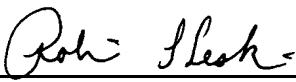
obtained, that they all exhibited different properties, e.g., different binding affinities, as well as different epitopic binding specificities to the gp39 protein. The fact that these antibodies possess different binding characteristics is also substantiated by the results contained in Table 4.

Therefore, based on the foregoing, applicants respectfully submit that the prior art cited in the Office Action, would not fairly teach or suggest the two specific deposited monoclonal antibodies or corresponding cell lines. Nor would the prior art fairly suggest monoclonal antibodies that specifically inhibit the binding of these antibodies to the corresponding epithet on gp39.

Based on the foregoing, this application is believed to be in condition for allowance. A notice to that effect is respectfully solicited. However, if any issues remain outstanding after consideration of this reply the Examiner is respectfully requested to contact the undersigned so that prosecution of this application may be expedited.

Respectfully submitted,

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Manual of Patent Examining Procedure, Section 713.04 Substance of Interview must Be Made of Record

A complete written statement as to the substance of any face-to-face or telephone interview with regard to an application must be made of record in the application, whether or not an agreement with the examiner was reached at the interview.

§1.133 Interviews

(b) In every instance where reconsideration is requested in view of an interview with an examiner, a complete written statement of the reasons presented at the interview as warranting favorable action must be filed by the applicant. An interview does not remove the necessity for response to Office action as specified in §§ 1.111, 1.135. (35 U.S.C. 132)

§ 1.2. Business to be transacted in writing. All business with the Patent or Trademark Office should be transacted in writing. The personal attendance of applicants or their attorneys or agents at the Patent and Trademark Office is unnecessary. The action of the Patent and Trademark Office will be based exclusively on the written record in the Office. No attention will be paid to any alleged oral promise, stipulation, or understanding in relation to which there is disagreement or doubt.

The action of the Patent and Trademark Office cannot be based exclusively on the written record in the Office if that record is itself incomplete through the failure to record the substance of interviews.

It is the responsibility of the applicant or the attorney or agent to make the substance of an interview of record in the application file, unless the examiner indicates he or she will do so. It is the examiner's responsibility to see that such a record is made and to correct material inaccuracies which bear directly on the question of patentability.

Examiners must complete a two-sheet carbon interleaf Interview Summary Form for each interview held after January 1, 1978 where a matter of substance has been discussed during the interview by checking the appropriate boxes and filling in the blanks in neat handwritten form using a ball point pen. Discussions regarding only procedural matters, directed solely to restriction requirements for which interview recordation is otherwise provided for in Section 812.01 of the Manual of Patent Examining Procedure, or pointing out typographical errors or unreadable script in Office actions or the like, are excluded from the interview recordation procedures below.

The Interview Summary Form shall be given an appropriate paper number, placed in the right hand portion of the file, and listed on the "Contents" list on the file wrapper. The docket and serial register cards need not be updated to reflect interviews. In a personal interview, the duplicate copy of the Form is removed and given to the applicant (or attorney or agent) at the conclusion of the interview. In the case of a telephonic interview, the copy is mailed to the applicant's correspondence address either with or prior to the next official communication. If additional correspondence from the examiner is not likely before an allowance or if other circumstances dictate, the Form should be mailed promptly after the telephonic interview rather than with the next official communication.

The Form provides for recordation of the following information:

- Serial Number of the application
- Name of applicant
- Name of examiner
- Date of interview
- Type of interview (personal or telephonic)
- Name of participant(s) (applicant, attorney or agent, etc.)
- An indication whether or not an exhibit was shown or a demonstration conducted
- An identification of the claims discussed
- An identification of the specific prior art discussed
- An indication whether an agreement was reached and if so, a description of the general nature of the agreement (may be by attachment of a copy of amendments or claims agreed as being allowable). (Agreements as to allowability are tentative and do not restrict further action by the examiner to the contrary.)
- The signature of the examiner who conducted the interview
- Names of other Patent and Trademark Office personnel present.

The Form also contains a statement reminding the applicant of his responsibility to record the substance of the interview.

It is desirable that the examiner orally remind the applicant of his obligation to record the substance of the interview in each case unless both applicant and examiner agree that the examiner will record same. Where the examiner agrees to record the substance of the interview, or when it is adequately recorded on the Form or in an attachment to the Form, the examiner should check a box at the bottom of the Form informing the applicant that he need not supplement the Form by submitting a separate record of the substance of the interview.

It should be noted, however, that the Interview Summary Form will not normally be considered a complete and proper recordation of the interview unless it includes, or is supplemented by the applicant or the examiner to include, all of the applicable items required below concerning the substance of the interview:

A complete and proper recordation of the substance of any interview should include at least the following applicable items:

- 1) A brief description of the nature of any exhibit shown or any demonstration conducted,
- 2) an identification of the claims discussed,
- 3) an identification of specific prior art discussed,
- 4) an identification of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the examiner,
- 5) a brief identification of the general thrust of the principal arguments presented to the examiner. The identification of arguments need not be lengthy or elaborate. A verbatim or highly detailed description of the arguments is not required. The identification of the arguments is sufficient if the general nature or thrust of the principal arguments made to the examiner can be understood in the context of the application file. Of course, the applicant may desire to emphasize and fully describe those arguments which he feels were or might be persuasive to the examiner,
- 6) a general indication of any other pertinent matters discussed, and
- 7) if appropriate, the general results or outcome of the interview unless already described in the Interview Summary Form completed by the examiner.

Examiners are expected to carefully review the applicant's record of the substance of an interview. If the record is not complete or accurate, the examiner will give the applicant one month from the date of the notifying letter or the remainder of any period for response, whichever is longer, to complete the response and thereby avoid abandonment of the application (37 CFR 1.135(c)).

Examiner to Check for Accuracy

Applicant's summary of what took place at the interview should be carefully checked to determine the accuracy of any argument or statement attributed to the examiner during the interview. If there is an inaccuracy and it bears directly on the question of patentability, it should be pointed out in the next Office letter. If the claims are allowable for other reasons of record, the examiner should send a letter setting forth his or her version of the statement attributed to him. If the record is complete and accurate, the examiner should place the indication "Interview record OK" on the paper recording the substance of the interview along with the date and the examiner's initials.